Cost-effectiveness of bevacizumab for diabetic macular oedema

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Abstract

We built a Markov model to predict the outcomes and cost-effectiveness of bevacizumab compared to macular laser therapy for diabetes patients with clinically significant macular oedema (CSMO). We used outcome data from an RCT, utility data and health states from a ranibizumab health technology assessment (HTA), and costs from the UK National Tariff.

37.73% of patients treated with bevacizumab in the model had a visual acuity of at least 76 ETDRS letters after four years, compared with 4.09% of laser therapy patients. Also, only 0.11% of bevacizumab patients were blind after four years, compared with 6.45% of laser therapy patients. However, with an ICER of £51,182, we predict that bevacizumab would not be cost-effective compared to laser therapy because of the influence of the NHS national tariff costs for monitoring patients and administering bevacizumab, and the EQ-5D's inability to sufficiently capture the impact of sensory deprivation on quality of life. We therefore advise significant caution when interpreting the results of cost-effectiveness analyses of interventions that involve vision-related interventions.

Key Points

- We undertook a cost-effectiveness analysis of bevacizumab compared to laser therapy for treating Diabetic Macular Oedema
- Our model predicts that bevacizumab would lead to significant improvements to visual acuity for patients
- Our model also predicts that bevacizumab is not considered to be cost-effective because of but the inadequacy of conventional quality of life measures to capture the impact on quality of life of sensory deprivation
- We would advise caution when interpreting results of cost-effectiveness analyses that assess vision-related interventions
- We strongly encourage the research, development and uptake of quality of life measures that adequately capture the impact of sensory deprivation on quality of life

Introduction

Diabetic Macular Oedema (DMO) has been treated for many years with macular laser therapy (MLT), which is largely successful at slowing the deterioration of visual acuity (Early Treatment Diabetic Retinopathy Study Research Group, 1985). However, there are concerns that laser therapy is, effectively, a destructive intervention which can cause scarring, and can lead to further deterioration of visual acuity if the laser scars enlarge (Schatz et al, 1991). Furthermore, some patients are unable to receive or be fully treated with laser therapy because the oedema involves the fovea, or are otherwise refractory to laser (Bailey et al, 1999). This has prompted an interest in alternative treatments for DMO. Anti-VEGFs such as ranibizumab and bevacizumab may offer a means to improve visual acuity (Mitchell et al, 2012; Rajendram et al, 2012), and treat patients who are refractory to laser, or for whom laser cannot be used to remove all of the oedema.

The cost-effectiveness of ranibizumab for the treatment of DMO has been previously reported (Mitchell et al, 2012), and is now recommended by the National Institute for Health and Care Excellence (NICE) following an initial decision not to recommend the drug (NICE, 2013). Whilst the details of the revised Patient Access Scheme are confidential, generally bevacizumab is a much cheaper drug than ranibizumab (Raftery et al, 2007), and therefore may represent a more cost-effective alternative treatment. The BOLT (Bevacizumab or Laser Therapy) study (Michaelides et al, 2010; Rajendram et al, 2012) was a two-year randomised controlled trial that compared the visual acuity outcomes of two groups of patients with centre-involved clinically significant macular oedema (CSMO), one of which was treated with bevacizumab and one with macular laser therapy. The study reports a mean gain of 8.6 ETDRS (Early Treatment Diabetic Retinopathy Study) letters for the bevacizumab group, compared to a mean loss of 0.5 ETDRS letters for the laser therapy group.

In this study, we report the findings from a cost-effectiveness analysis of bevacizumab for the treatment of DMO, compared with macular laser therapy. We use the reported two-year outcomes

from the BOLT study, along with costs from the UK NHS cost schedule (Department of Health, 2012) and utilities and health states from the ranibizumab for DMO cost-effectiveness analysis (Mitchell et al, 2012). We predict the visual acuity outcomes and cost-effectiveness over a four year period for both treatments, which represents a trade-off between minimising the period of time for which we do not have effectiveness data, and allowing sufficient time for cost and quality of life benefits to emerge. Furthermore, we demonstrate that bevacizumab is not considered to be cost-effective in such an analysis, in part due to the inability to adequately capture the impact on vision-impacted quality of life in such analyses.

Methods

Introduction to Methods

We developed a Markov model to assess the incremental expected costs and quality of life of bevacizumab for the treatment of DMO, compared with macular laser therapy. In a Markov model, patients move through various health states, which correspond to the progression of a disease, or complications that can arise. In our model, two cohorts of 100,000 CSMO patients progress over a four-year time horizon, with time progressing in 28-day cycles. One cohort is assigned to receive bevacizumab treatment, whilst the other receives macular laser therapy.

Each health state is assigned an associated utility, which attempts to quantify a patient's quality of life when they are in this health state. In addition, a health state may have associated costs for treatment, support and monitoring. Our model adopted the perspective of the NHS and Personal Social Services, and therefore only these costs were included.

Health States

Since we are determining patient outcomes in terms of visual acuity, the health states in our model represent various levels of visual acuity, specified in terms of an assessment of ETDRS best-corrected

visual acuity (BCVA). Specifically, we use the health states implemented by the ranibizumab for DMO cost-effectiveness analysis (Mitchell et al, 2012), in which each health state represents a 10-letter range of visual acuity, except for the lowest (≤ 25 letters) and highest (86-100 letters). The health state representing a visual acuity of ≤ 25 letters corresponds to patients who are blind (WHO, 2010), and patients in this health state cannot improve in the model, as they receive no further treatment. We also have an additional health state to represent patients who have died ("Death"). Figure 1 shows the health states used in our model, and the possible transitions between them for each 28 day cycle. At the start of the model, all patients have visual acuities between 36 and 75 ETDRS letters - approximating the baseline characteristics of the BOLT study (Michaelides et al, 2010) - and are distributed uniformly across the four health states in this range.

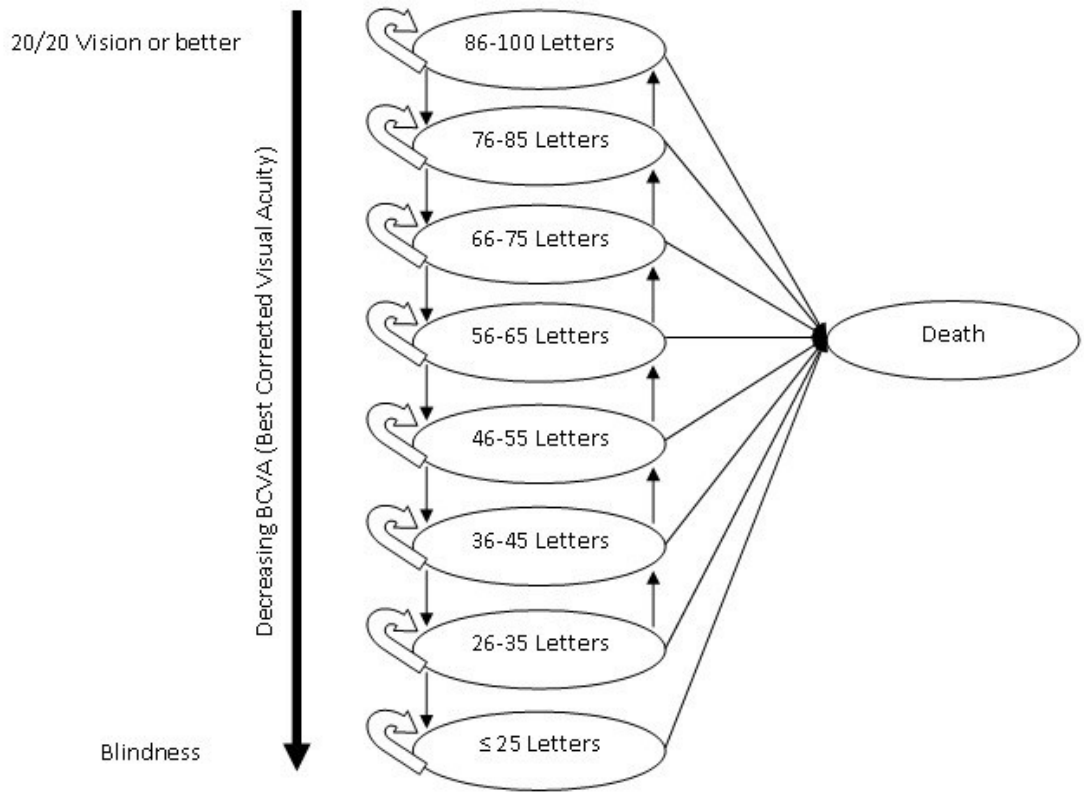

Figure 1. Health states in the model and the potential transitions between them.

Utilities

Utility values weight the time spent in health states according to the expected quality of life associated with being in that health state. We explored a number of alternatives to determine the utility levels appropriate for each health state in our model (Brown et al, 1999; Misajon et al, 2005; Lloyd et al, 2008). Vision-specific quality of life measures potentially offer a means of better capturing aspects of sensory deprivation than traditional MAU models such as the EQ-5D (Misajon et al, 2005; Lloyd et al, 2008), but measures such as the VisQoL (Misajon et al, 2005) are sparsely referenced in the literature, and seem to have a poor uptake. We therefore used the utility scores provided by Mitchell et al (Mitchell et al, 2012) to populate the utility scores in our model (Table 1), which were derived from EQ-5D scores in the RESTORE trial, and then converted to represent a UK population. Using EQ-5D scores is the preferred approach of NICE (NICE, 2008), and the study demonstrated that the scores derived were similar to those found in the Brown et al (1999) and Lloyd et al (2008) studies.

Treatment and Monitoring Regimens

The treatment and monitoring regimens used in the model are based on the BOLT study (Rajendram et al, 2012), with some amendments made in consultation with local clinicians to better approximate clinical practice in the UK. Patients treated with bevacizumab receive a 1.25mg dose of the drug in each injection, and are monitored and assessed for treatment every six weeks. BOLT reports that the median number of injections received per patient in the first year was nine, and in the second year was four. Therefore, patients in our model receive an injection at baseline and every six weeks thereafter in the first year, and every 12 weeks in the second year.

Patients treated with macular laser therapy are monitored and assessed for treatment every three months. BOLT reports that patients attended a median of three laser therapy sessions in the first year, and just one in the second year. Therefore, in our model, patients receive laser therapy at baseline, at six months and at 12 months in year one, and six months into year two. For both the bevacizumab

and laser therapy regimens, we assume that the treatment frequency for years three and four is the same as year two.

Outcomes

The BOLT study reports the two-year visual acuity outcomes in terms of visual acuity changes from baseline. We find that, within two years, for those treated with bevacizumab : (i) 32% gained at least 15 ETDRS letters, (ii) 17% gained between 10 and 14 ETDRS letters, and (iii) 51% gained less than 10 ETDRS letters or lost less than 15 ETDRS letters.

We assume that 95% of the 'stabilisation' group (the 51% that gained less than 10 letters or lost less than 15 letters) gained or lost less than 10 letters, which would result in no change in health state in our model. This implies that 2.6% of patients lost between 10 and 14 letters (inclusive), which is similar to the visual acuity deterioration rate of 3.5% observed with ranibizumab treatment (European Medicines Agency, 2011).

For laser therapy, we find that, within two years, (i) 4% gained at least 15 ETDRS letters, (ii) 3% gained between 10 and 14 ETDRS letters, (iii) 79% gained less than 10 ETDRS letters or lost less than 15 ETDRS letters, and (iv) 14% lost 15 ETDRS letters or more. Again, we assume that 95% of the 'stabilisation' group gained or lost less than 10 letters, which implies that 3.95% of patients lost between 10 and 14 letters (inclusive), similar to the 5% deterioration rate reported by a Diabetic Retinopathy Clinical Research Network (DRCRN) study (Elman et al, 2010).

For simplicity, we assume that a gain or loss of at least 15 letters translates to a gain or loss of two health states in the model.

Mortality

The mortality rate for patients in the model was taken from the ranibizumab HTA by Mitchell et al (Mitchell et al, 2012). Specifically, patients in the model are 2.45 times more likely to die than their same-age, same-gender equivalents in the general population. This risk ratio incorporates the increased risk of death from type 2 diabetes, and the increased risk of death from CSMO. Background mortality rates were taken from UK Interim Life Tables (Office for National Statistics, 2009). The cohort of patients used to initially populate the model are aged 64, and 69% of them are male (Michaelides et al, 2010).

Adverse Events

Bevacizumab is associated with a range of minor injection-related adverse events, such as red-eye and irritation (Michaelides et al, 2010; Rajendram et al, 2012), but these do not typically prevent further treatment for the patient or affect the patient's long-term quality of life, and are therefore excluded from our model. Patients treated with bevacizumab have a small risk of developing retinal detachment, estimated to affect around 0.19% of bevacizumab patients within one year (Wu et al, 2008). It is expected that around 85% of patients who develop retinal detachment would be successfully treated with a vitrectomy (James et al, 2002). Whilst the remaining 15% would normally undergo a second procedure (James et al, 2002), for simplification we here assume that these patients for whom the first procedure was unsuccessful lose their vision (Flynn et al, 1992) (visual acuity of 25 ETDRS letters or fewer). We also assume that patients who suffer from vitreous haemorrhage lose their vision (Flynn et al, 1992), as the risk of this adverse event for patients treated with bevacizumab is very small, at around 0.02% within one year (Wu et al, 2008).

Patients treated with macular laser therapy may suffer from laser burn causing scarring, and the enlargement of laser scars can affect visual acuity (Schatz et al, 1991). The BOLT study reports that

14% of patients treated with macular laser therapy lost 15 ETDRS letters or more within two years (Rajendram et al, 2012), and we implement this as a probability of deteriorating by two health states in our model. It is likely that at least a proportion of these patients in the BOLT study significantly lost their vision because of laser scar enlargement, as studies have found that around 5% of laser-treated patients are affected by this (Schatz et al, 1991; Rutledge et al, 1993).

Costs

We derived costs from the UK National Tariff of healthcare costs for 2011-2012 (Department of Health, 2012), and based our estimates of resource usage on the opinion of local clinicians. Table 2 provides details of the costs used in the model. A 3.5% annual discount rate is applied to costs and benefits in the model.

Results

In our model, 37.73% of the 100,000 patients treated with bevacizumab had a visual acuity of at least 75 ETDRS letters after four years, compared with just 4.09% of patients treated with macular laser therapy. In addition, only 0.11% of bevacizumab patients were 'blind' (visual acuity of 25 ETDRS letters or fewer) after four years, compared to 6.45% of laser therapy patients. The distribution of visual acuity outcomes after four years for both treatments is shown in figure 2.

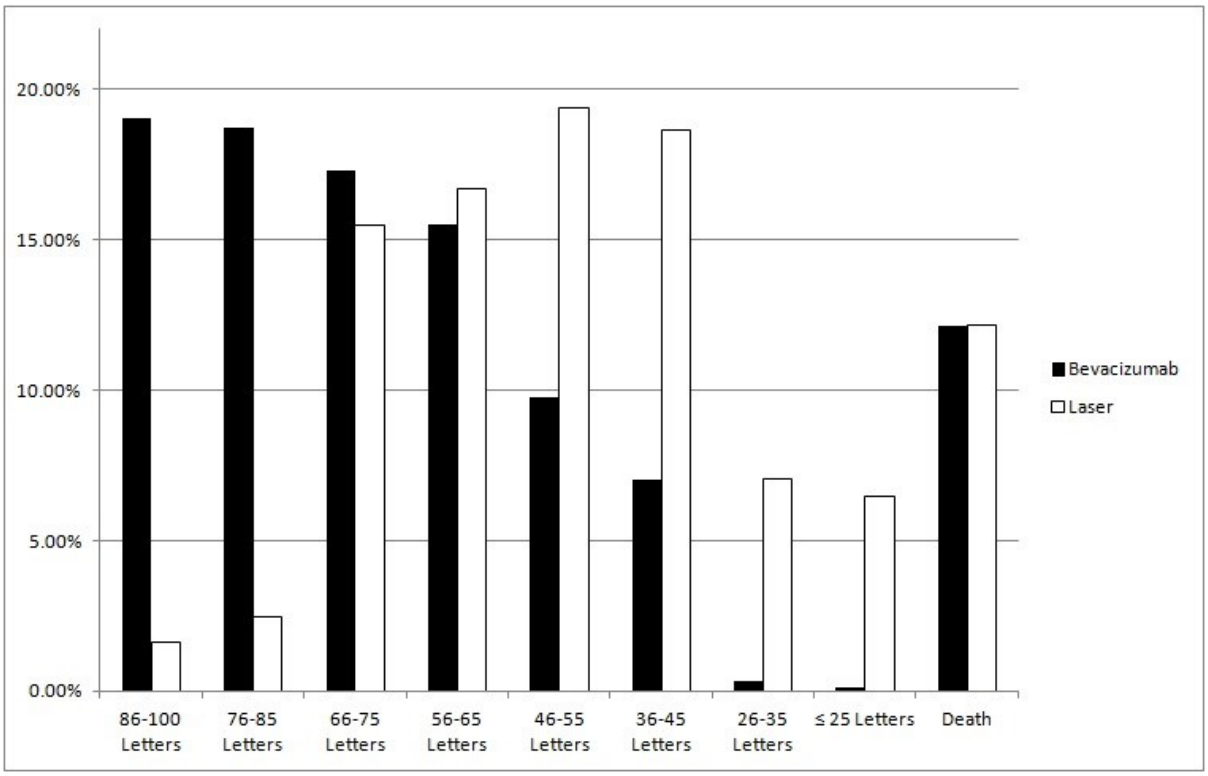

Figure 2. Distribution of patients across the nine health states in the model after four years have elapsed, comparing bevacizumab-treated patients with macular laser therapy-treated patients.

There is a large difference in costs between the two treatments, as we predict that bevacizumab would cost the NHS £5,503.88 more per patient over four years. We predict the difference in utilities to be relatively minor, with a gain of just 0.1075 QALYs per patient for bevacizumab compared to laser therapy. The incremental cost-effectiveness ratio (ICER) for bevacizumab compared with macular laser therapy is £51,182 per QALY. Therefore, bevacizumab is unlikely to be considered cost-effective compared to laser therapy using the standard NICE willingness-to-pay range of £20,000 to £30,000 per QALY (NICE, 2008). Table 3 provides a detailed breakdown of the marginal costs and utilities between the bevacizumab and laser therapy treatments.

Discussion

Whilst we predict that bevacizumab would lead to significantly improved clinical outcomes within four years for patients with Diabetic Macular Oedema, which could lead to important quality of life changes such as the ability to drive, we found that our cost-effectiveness results did not reflect this. Atypically for a cost-effectiveness analysis, the majority of the cost associated with bevacizumab treatment is for the intravitreal administration of the drug and monitoring, rather than the drug itself.

We also found only a small gain in Quality Adjusted Life Years (QALYs) when using bevacizumab compared to laser therapy, despite the model's prediction that significantly fewer patients would lose their vision when treated with bevacizumab, and significantly more patients would regain the best levels of visual acuity. It has been argued that measures such as the EQ-5D do not sufficiently capture aspects of sensory deprivation (Misajon et al, 2005; Lloyd et al, 2008), and therefore may not adequately quantify the quality of life of diabetic macular oedema patients living with visual impairment. Additionally, local clinicians advised us that they would have expected to see a much more pronounced deterioration in utility values after a patient drops below 76 letters of visual acuity, because it is at this stage that patients lose the ability to drive and to carry out other everyday tasks. We would therefore strongly encourage the development and utilisation of measures that can better represent the impact of eye disease on a patient's quality of life.

In conclusion, our model predicts that bevacizumab is not a cost-effective treatment for diabetic macular oedema, compared to conventional macular laser therapy. The tariff costs of treatment and monitoring, coupled with the frequency of bevacizumab injections needed, and the regularity with which patients need to be monitored to promptly identify visual acuity deterioration, preclude a cost-effective treatment option. However, the significant visual acuity benefits of bevacizumab treatment seem to be underrepresented in the cost-effectiveness analysis, because of the inability of quality of life measures such as the EQ-5D to capture the impact of visual deterioration, which is the primary outcome of diabetic macular oedema. This has been a long recognised issue, and we believe it is time

that further research attempts to better quantify aspects of visual impairment in quality of life measures, in order to ensure that future cost-effectiveness analyses that assess interventions that affect visual acuity are more reliable and informative. In the meantime, we would advise caution when interpreting the results of any cost-effectiveness analysis that assesses vision-related interventions.

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Dr Daniel Chalk designed, implemented and tested the model, identified the literature to parameterise the model, and presented the model and results. Dr Martin Pitt (PenCLAHRC) provided guidance on the cost effectiveness analysis and model development. Professor Ken Stein oversaw the progress of the project, and offered guidance and feedback. All three authors contributed to the final manuscript. Dr Daniel Chalk had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors declare that they have no conflicts of interest.

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Tables

Table 1. Utility scores associated with each health state in the model. Utility scores derived from Mitchell et al (2012).

Health State	Utility Value
86-100 Letters	0.86
76-85 Letters	0.86
66-75 Letters	0.813
56-65 Letters	0.802
46-55 Letters	0.77
36-45 Letters	0.76
26-35 Letters	0.681
≤ 25 Letters	0.547
Death	0

Table 2. Details of the costs used in the model.

Description of Cost	Cost	Source(s)
Single 1.25mg dose of bevacizumab (pre-packaged 0.2ml syringe)	£48 + £2 delivery charge	Liverpool and Broadgreen NHS Manufacturing Unit
Bottle of post-injection eye drops (Chloramphenicol 0.5%)	£1.67	Department of Health, 2012
Intravitreal administration of bevacizumab	£145	UK National Tariff (Department of Health, 2012) (HRG BZ23Z Vitreous Retinal Procedures Category 1)
Single session of laser therapy	£145	UK National Tariff (Department of Health, 2012) (HRG BZ23Z Vitreous Retinal Procedures Category 1)
Initial outpatient monitoring visit (for either treatment)	£285	£112 consultant-led examination (Department of Health, 2012) £173 fluorescein angiography and tomography evaluation of the retina (HRG BZ23Z Vitreous Retinal Procedures Category 2)
Subsequent outpatient monitoring visit (for either treatment)	£210	£65 follow-up consultant-led examination (Department of Health, 2012) £145 Tomography evaluation of the retina (Department of Health, 2012) (HRG BZ23Z Vitreous Retinal Procedures Category 1)
Treating bevacizumab patient who has developed retinal detachment	£1,384	£1,124 vitrectomy using the pars plana approach (Department of Health, 2012) (BZ23Z Vitreous Retinal Procedures Category 2 (day case)) Four £65 follow-up ophthalmology visits (Department of Health, 2012)
Treating bevacizumab patient who has suffered vitreous haemorrhage	£1,254	£1,124 vitrectomy using the pars plana approach (Department of Health, 2012) (BZ23Z Vitreous Retinal Procedures Category 2 (day case)) Two £65 follow-up ophthalmology visits (Department of Health, 2012)
Cost of blindness (Patients with visual acuity of 25 ETDRS letters or fewer (WHO, 2010))	£6,477.22 per year per patient	Mitchell et al, 2012

Table 3. Details of the marginal costs and utilities between the bevacizumab and macular laser therapy treatments.

Health State	Discounted QALYs (Bevacizumab Pathway)	Discounted QALYs (Laser Therapy Pathway)	Difference in QALYs
86-100 Letters	31,286.33	3,105.36	28,180.97
76-85 Letters	35,412.52	4,628.91	30,783.61
66-75 Letters	67,176.09	61,806.83	5,369.26
56-65 Letters	64,172.61	63,184.87	987.74
46-55 Letters	48,488.13	65,406.62	-16,918.49
36-45 Letters	41,739.71	63,332.41	-21,592.70
26-35 Letters	746.14	10,026.83	-9,280.69
≤ 25 Letters	109.42	6,958.82	-6,849.40
Retinal Detachment	73.29	0	73.29
Death	0	0	0
Total	**289,204.24**	**278,450.65**	**10753.59**
Total (Per Person)	**2.8920**	**2.7845**	**0.1075**

Cost Description	Cost (Bevacizumab Pathway)	Cost (Laser Therapy Pathway)	Difference in Costs
Drug and administration cost	£372,552,473	£77,132,276	£295,420,197
Monitoring costs	£656,487,008	£322,043,233	£334,443,775
Cost of Adverse Event : Retinal Detachment	£646,251	£0	£646,251
Cost of Adverse Event : Vitreous Hemorrhage	£117,110	£0	£117,110
Cost of Adverse Event : Cataract Surgery Required	£0	£0	£0
Cost of Adverse Event : Glaucoma Medication Required	£0	£0	£0
Cost of Adverse Event : Sterile Endophthalmitis	£0	£0	£0
Cost of Blindness	£2,163,468	£82,402,274	-£80,238,806
Total	**£1,031,966,310**	**£481,577,784**	**£550,388,526**
Total (Per Person)	**£10,319.66**	**£4,815.78**	**£5,503.88**
Cost/QALY			**£51,182**